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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/938,940	08/24/2001	J. Bryan Jones	GC525-C3	3800

5100 7590 12/13/2002

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EXAMINER
HUTSON, RICHARD G

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 12/13/2002 8

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/938,940	JONES ET AL.	
	Examiner	Art Unit	
	Richard G Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-23,34 and 35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-23,34 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 August 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants preliminary amendment of canceling claims 1-13, 24-33 and 36, Paper No. 6, 9/30/2002, is acknowledged. Claims 14-23, 34 and 35 are still at issue and are present for examination.

Election/Restrictions

Applicant's election without traverse of Group II, Claims 14-23, 34 and 35 in Paper No. 6 is acknowledged.

Priority

Applicants statement on the first line of the specification that this application claims the benefit of U.S. Provisional Patent Application Serial No. 60/072,266, filed July 9, 1999 and International Application PCT/BE99/00152 filed January 23, 1998, which is hereby incorporated by reference is acknowledged. It is further noted that on applicants transmittal, applicant indicate that this application is a continuation of Application No. 09/234,956, filed January 21, 1999, which has issued as U.S. Patent No. 6,284,512 B1. It is suggested that the first line of the specification be amended to reflect this information.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper."

Applicants filing of information disclosures, Paper No. 3, filed 8/24/2001, is acknowledged. Those references considered have been initialed.

Drawings

The drawings filed on 8/24/2001 are objected to for the reasons stated on the enclosed form PTO-948. Note, applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14-23, 34 and 35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as

to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 14-23, 34 and 35 are directed to all possible chemically modified mutant enzymes with one or more amino acid residues replaced by a cysteine residue, wherein at least some of the cysteine residues are modified by replacing the thiol hydrogen in the cysteine residue with a thiol side chain, wherein the thiol side chain is selected from the group consisting of: $-SCH_2(p\text{-}CH_3\text{-}C_6H_4)$, $-SCH_2(p\text{-}OCH_3\text{-}C_6H_4)$, $-SCH_2(p\text{-}CF_3\text{-}C_6H_4)$ and $-SCH_2(2,4\text{-}diNO_2\text{-}C_6H_3)$. The specification, however, only provides the representative species of a chemically modified mutant *Bacillus lentus* subtilisin wherein the chemical modification corresponds to the replacement of amino acid residues N62, L217 and S166, with a cysteine residue, wherein the cysteine residue is modified by replacing the thiol hydrogen in the cysteine residue with a thiol side chain, wherein the thiol side chain is selected from the group consisting of: $-SCH_2(p\text{-}CH_3\text{-}C_6H_4)$, $-SCH_2(p\text{-}OCH_3\text{-}C_6H_4)$, $-SCH_2(p\text{-}CF_3\text{-}C_6H_4)$ and $-SCH_2(2,4\text{-}diNO_2\text{-}C_6H_3)$, encompassed by these claims. There is no disclosure of any particular structure to function/activity relationship in the disclosed species. The specification also fails to describe additional representative species of these enzymes by any identifying structural characteristics or properties other than the activities recited for the disclosed species, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would not recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 14-23, 34 and 35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a chemically modified mutant *Bacillus lentus* subtilisin wherein the chemical modification corresponds to the replacement of amino acid residues N62, L217 and S166, with a cysteine residue, wherein the cysteine residue is modified by replacing the thiol hydrogen in the cysteine residue with a thiol side chain, wherein the thiol side chain is selected from the group consisting of: -SCH_2(*p*-CH_3-C_6H_4), -SCH_2(*p*-OCH_3-C_6H_4), -SCH_2(*p*-CF_3-C_6H_4) and -SCH_2(2,4-diNO_2-C_6H_3), does not reasonably provide enablement for any chemically modified mutant enzyme with one or more amino acid residues replaced by a cysteine residue, wherein at least some of the cysteine residues are modified by replacing the thiol hydrogen in the cysteine residue with a thiol side chain, wherein the thiol side chain is selected from the group consisting of: -SCH_2(*p*-CH_3-C_6H_4), -SCH_2(*p*-OCH_3-C_6H_4), -SCH_2(*p*-CF_3-C_6H_4) and -SCH_2(2,4-diNO_2-C_6H_3). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of

direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 14-23, 34 and 35 are so broad as to encompass any chemically modified mutant enzyme with one or more amino acid residues replaced by a cysteine residue, wherein at least some of the cysteine residues are modified by replacing the thiol hydrogen in the cysteine residue with a thiol side chain, wherein the thiol side chain is selected from the group consisting of: -SCH_2(*p*-CH_3-C_6H_4), -SCH_2(*p*-OCH_3-C_6H_4), -SCH_2(*p*-CF_3-C_6H_4) and -SCH_2(2,4-diNO_2-C_6H_3). The scope of the claim is not commensurate with the enablement provided by the disclosure with regard to the utility of the extremely large number of enzymes broadly encompassed by the claims. It would require undue experimentation of the skilled artisan to make and use the claimed enzymes with any activity, including any protease activity (claims 15 and 16). The specification is limited to teaching use of the chemically modified mutant *Bacillus lentus* subtilisin with one or more amino acid residues corresponding to N62, L217 and S166 replaced by a cysteine residue, wherein the cysteine residue is modified by replacing the thiol hydrogen in the cysteine residue with a thiol side chain, wherein the thiol side chain is selected from the group consisting of: -SCH_2(*p*-CH_3-C_6H_4), -SCH_2(*p*-OCH_3-C_6H_4), -SCH_2(*p*-CF_3-C_6H_4) and -SCH_2(2,4-diNO_2-C_6H_3), as having an increased esterase/amidase activity ratio for use in peptide synthesis and provides no guidance with regard to other uses or means of making other enzymes encompassed by the

claims. In view of the great breadth of the claims, amount of experimentation required to make the claimed mutant enzymes, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to make and use the full scope of the chemically modified mutant enzymes, wherein one or more amino acid residues are replaced by a cysteine residue having the thiol hydrogen in the cysteine residue replaced with a thiol side chain, wherein the thiol side chain is selected from the group consisting of: -SCH_2(*p*-CH_3-C_6H_4), -SCH_2(*p*-OCH_3-C_6H_4), -SCH_2(*p*-CF_3-C_6H_4) and -SCH_2(2,4-diNO_2-C_6H_3) encompassed by this claim

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any of the claimed chemically modified mutant enzymes having any activity or function. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claim 16 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim1 of prior U.S. Patent No. 6,284,512 B1. This is a double patenting rejection.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 14, 15, 17-23, 34 and 35 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8, 9 and 10 of U.S. Patent No. 6,284,512 B1. Although the conflicting claims are not identical, they

are not patentably distinct from each other because claims 1-8, 9 and 10 of U.S. Patent No. 6,284,512 B1 anticipate claims 14, 15, 17-23, 34 and 35, respectively.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard Hutson, Ph.D.
Patent Examiner
Art Unit 1652
December 12, 2002